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HUMAN SLEEP AND ITS REGULATION

Sleep is a ubiquitous state which has been described for (almost) all species studied, ranging from cockroaches to humans (ZIMMERMAN *et al.* 2008, TOBLER 2011). The behavioral criteria for the definition of sleep are listed in Table 1. Sleep homeostasis was subsequently added to the behavioral definition of sleep (Table 1) (TOBLER 1984). Homeostasis was defined as a biological principle by CANNON in 1939 as "the coordinated physiologic processes which maintain most of the steady states in the organism". Applied to sleep, an animal deprived of sleep must compensate for sleep loss through sleeping for a longer duration or with higher intensity. This concept is referred to as sleep homeostasis and was originally coined by BORBÉLY in 1980. In this article we will describe the ways in which sleep homeostasis can be measured in humans and its implications for behavior. But first, a brief detour to describe how we measure sleep.

Electrophysiological criteria for the transition from waking to sleep (Table 2) are based on cortical activity (measured by the electroencephalogram, EEG), eye movements (measured by the electrocoulogram, EOG) and muscle tone (electromyogram, EMG). There are many methods to measure sleep in humans, however, polysomonography (PSG) remains the gold standard by which we quantify sleep. PSG is a physiological measure of sleep and is based on the EEG, EOG, and EMG. Dependent on the question addressed, additional variables such as heartbeat (measured by the electrocardiogram, ECG), leg movements or respiratory variables are also measured. Based on the EEG, EOG, and EMG, it is possible to divide sleep into five stages. Stages one to four

Table 1. Behavioral criteria for the definition of sleep (PIÉRON 1913; FLANIGAN *et al.* 1974; TOBLER 1984)

Specific sleeping site
Species specific body position
Immobility
Elevated arousal and reactivity threshold
Fast reversibility
Compensation of a sleep deficit (homeostatic regulation)

Table 2. Electrophysiological criteria for the definition of sleep (TOBLER 1984). Changes from wakefulness to sleep are summarized.

Electroencephalogram (EEG)	Low voltage fast waves →
	spindles
	high voltage slow waves
Electrooculogram (EOG)	Eye movements, eye blinks →
	absence of eye movements in non-REM sleep
	rapid eye movements in REM sleep
Electromyogram (EMG)	Progressive loss of muscle tone from wake to non-REM sleep to REM sleep

are often collectively termed non-rapid eye movement (non-REM) sleep, while the fifth stage is called REM sleep. The progression through the different stages is not random, but rather follows a pattern with sleep progressing through stages 1 to 4 to REM sleep and then back to stage 1 (Fig. 1, top panel). This progression typically takes 90 to 120 minutes in adults and is called a sleep cycle. Thus, an 8-hour night of sleep in an adult will consist of upwards of three cycles. Furthermore, sleep stages are not evenly distributed throughout the night. At the beginning of sleep, stages 3 and 4, collectively called

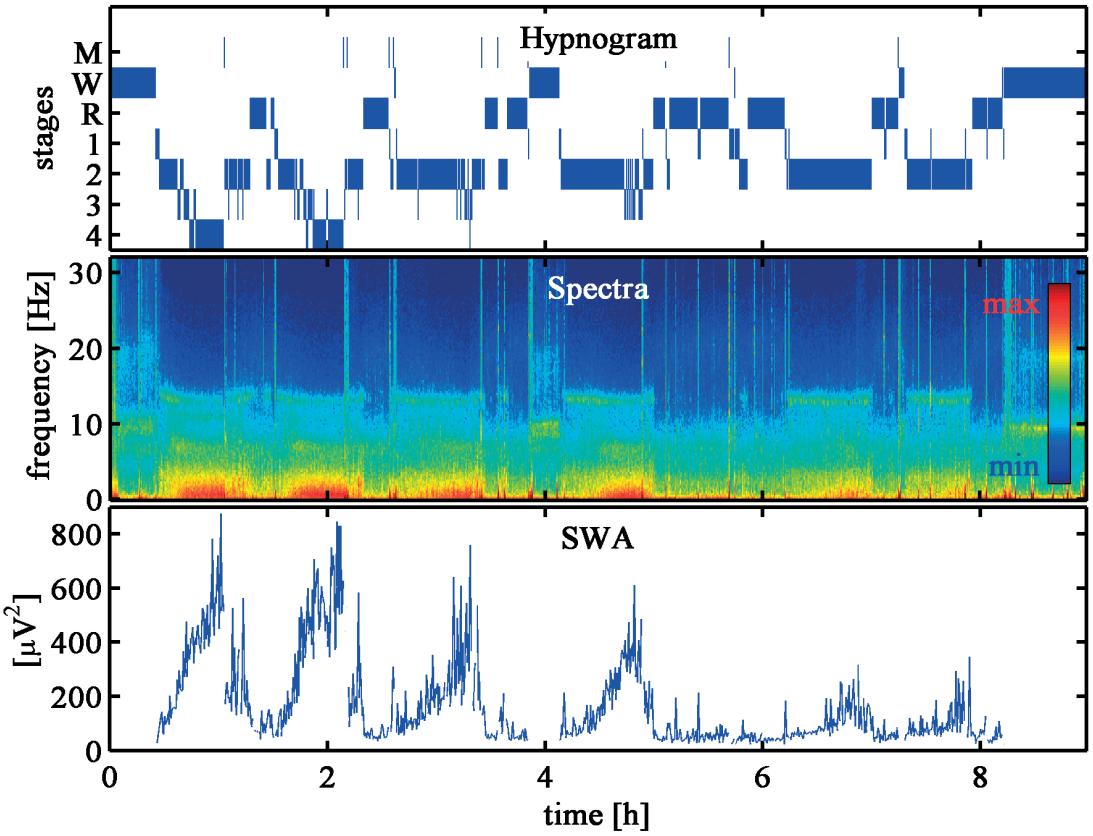

Figure 1. Sleep profile (top, hypnogram), spectrogram (middle; color-coded power density spectra on a logarithmic scale of consecutive 30-s epochs; FFT, Tukey window (r=0.5), average of ten 4-s epochs overlapping by 1 s) and slow-wave activity (bottom; SWA; power in 0.75-4.5 Hz range). Sleep stages were visually scored for 30-s epochs (W: waking; M: movement time; R: REM sleep; 1 to 4: non-REM sleep stages 1 to 4; Figure 1.3 of RUSTERHOLZ 2011).

slow wave sleep (SWS) are more frequent and the duration spent in this sleep state progressively declines through the course of a night (Fig. 1, top panel). Slow wave sleep is defined by the presence of low frequency, high amplitude waves, called slow waves. Another readily observable characteristic of sleep across the night is the progressive lengthening of REM sleep. REM sleep episodes are brief at the beginning of the night and typically reach their longest duration at the end of the night. Characteristic changes across a sleep episode are also observed in other physiological variables such as body temperature, heart rate and muscle tone (Fig. 2).

In addition to quantifying a night of sleep using sleep stage variables, various mathematical transforms can be applied to the EEG signal to summarize the cortical oscillations present during sleep. The most commonly used methods are variants of the

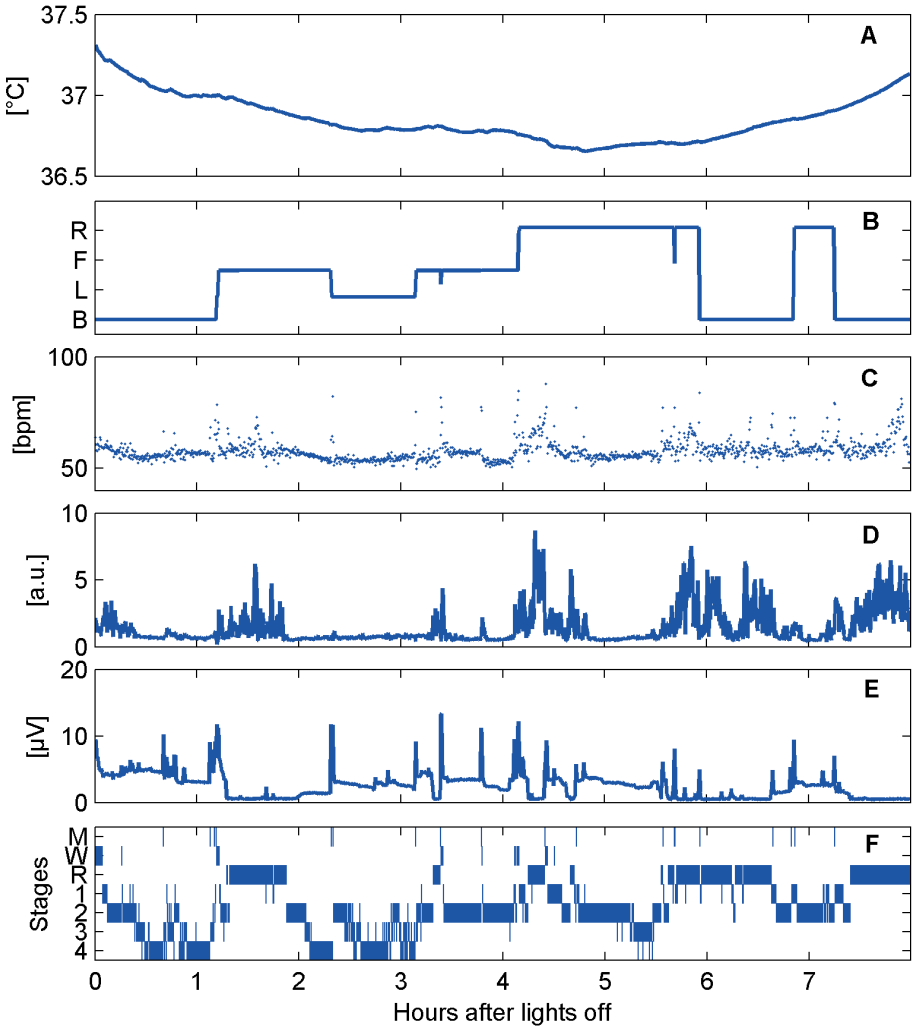

Figure 2. Characteristic variations in the course of sleep are observed not only in the EEG, but also in other measures.

Body temperature (A) decreases until a minimum is reached in the second half of the night, and then increases again. Body position (B; L: left, R: right, B: back; F: front (belly)) may change more or less frequently; in this healthy young male who slept well, the number of body position changes was small. Heart rate (C; beats per min [bpm]) is generally increased and more variable during REM sleep than in non-REM sleep. Heart rate during sleep is lower than during wake. Eye movements (D; quantified as ratio of mean EOG and EEG amplitude) occur not only in REM sleep, but also at the beginning of a sleep episode (slow eye movements). Muscle tone (E; mean EMG amplitude in 15.6-54 Hz range) is low during REM sleep episodes. The sleep profile (F; hypnogram; M: movement time; W: waking; R: REM sleep; 1 to 4: non-REM sleep stages 1 to 4) is provided at the bottom.

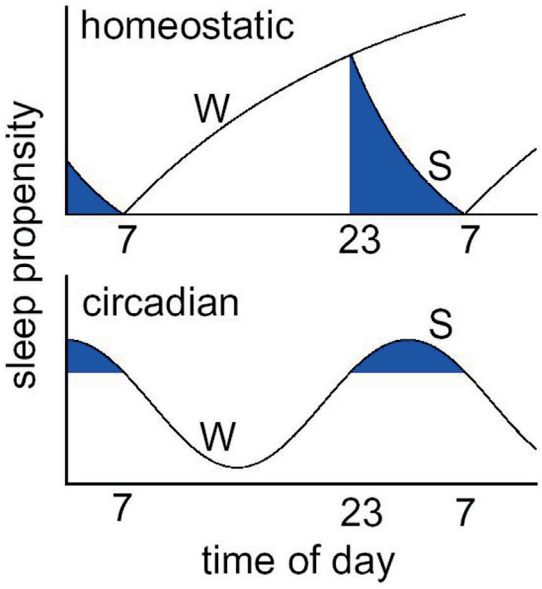

Figure 3. Schematic representation of the two major processes underlying sleep regulation: a homeostatic (sleep wake dependent) and a circadian (sleep wake independent) process. W, waking; S, sleep.

Fourier transform — a mathematical way to decompose a signal into its constituent frequency components. The fast Fourier transform (FFT) is a widely applied method for obtaining the EEG power density spectra. The spectrogram (i.e. color-coded power density spectra) of an entire nights' sleep provides a clear overview of the structure of sleep even if sleep stages have not yet been visually scored (Fig. 1, middle panel). One frequency range that is of particular interest to sleep researchers is the delta band, also referred to as slow-wave activity (SWA), ranging in frequency between approximately 0.5 to 4.5 Hz. It was recognized early on that sleep intensity is reflected in the sleep EEG by the prevalence of low frequency, high amplitude waves called slow waves (BLAKE and GERARD 1937). Under normal physiological conditions, slow waves in the non-REM sleep EEG can be regarded as an indicator of "sleep depth" or "sleep intensity". Furthermore, power in the delta band is a key marker of homeostatic sleep pressure – increasing with time awake and dissipating during sleep (Fig. 1, bottom panel; Fig. 4).

The most prominent model of sleep regulation is the two-process model, first described by BORBÉLY in 1982. In this model, two processes — a circadian process, C and a homeostatic process, S — interact to determine the timing of sleep and wakefulness (BORBÉLY 1982, DAAN *et al.* 1984, ACHERMANN and BORBÉLY 2011). Process C, called the circadian component, is independent of prior wakefulness and oscillates with a rhythm of approximately 24 hours (Fig. 3, bottom panel). Process S, or the homeostatic component, is dependent on prior wakefulness, building up during waking and dissipating during sleep (Fig. 3, top panel). These processes work together to ensure consolidated sleep at night and maximal alertness during the day.

The homeostatic process S may be modeled by two exponential functions — one for the sleep and one for the wake state. The buildup of sleep pressure during waking is described with a saturating exponential function (equation 1; Fig. 4) while the dissipation of sleep pressure during sleep is exponential (equation 2; Fig. 4).

$$S(t) = (S_{WU} - UA) * \exp\left(-\frac{t}{\tau_i}\right) + UA \qquad \text{during wake} \qquad (1)$$

$$S(t) = (S_{SO} - LA) * \exp\left(-\frac{t}{\tau_d}\right) + LA \qquad \text{during sleep} \qquad (2)$$

In the above equations τ_i is the time constant of the increasing saturating exponential function during wake, τ_d is the time constant of the decreasing exponential function during sleep, *UA* is the upper asymptote, *LA* is the lower asymptote, S_{WU} is the level of S at wake up, S_{SO} is the level of *S* at sleep onset, and *t* is time, starting at zero with wake up or with sleep onset, respectively. Thus, process S oscillates between an upper and lower asymptote. Its dynamics are governed by the distance between the asymptotes and the time constants (Fig. 4). The time constants show significant inter-individual variability (RUSTERHOLZ *et al.* 2010) in addition to varying across brain regions, with longer time constants observed in anterior compared to posterior regions (RUSTERHOLZ and ACHERMANN 2011). Homeostasis is mainly reflected in the time constants and those with a slower buildup might tolerate sleep deprivation better (RUSTERHOLZ *et al.* 2010). Furthermore, the distance between the asymptotes may be interpreted as the capacity of the brain to generate slow waves (JENNI *et al.* 2005, RUSTERHOLZ *et al.* 2010).

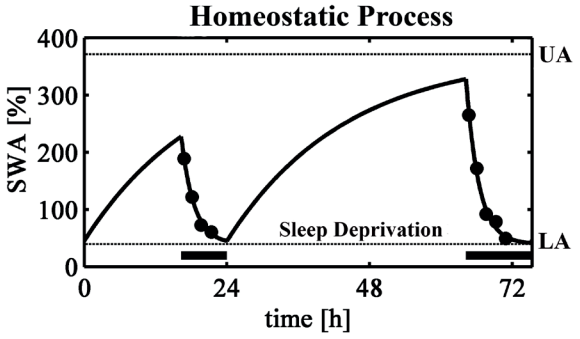

Figure 4. Build-up and dissipation of the homeostatic process S.

The left portion of the plot (0 to 24 hours) shows the build-up of sleep pressure over 16 hours of wakefulness followed by its dissipation over 8 hours of sleep. The right portion of the plot (24 to 72 hours) depicts the build-up of sleep pressure during prolonged wakefulness of 40 hours (sleep deprivation) and the subsequent dissipation of sleep pressure during the recovery sleep. Black bars at the bottom indicate sleep episodes. Dots: Empirical mean normalized slow-wave activity (SWA) per non-REM sleep episode (8 subjects) plotted at episode midpoints for baseline and a recovery sleep. Curve: Simulation of the homeostatic process S. UA: Upper asymptote; LA: lower asymptote. For the equations see text (equations 1 and 2).

With regards to SWA, it is important to remember that the absolute values of SWA are highly variable across participants and in large part dependent on age (TAROKH and ACHERMANN 2013). For example, SWA in young children is several orders of magnitude larger than in young adults and correlated also with grey matter volume (BUCHMANN *et al.* 2011). Thus, absolute SWA is not a measure of sleep pressure or homeostasis per se, but rather it is the relative change in SWA in response to a challenge that is informative (e.g., total or partial sleep deprivation, sleep restriction, naps).

Sleep is crucial for day-time functioning and well-being. Nevertheless, its biological function remains a mystery. However, as Allan Rechtschaffen, a prominent sleep researcher, has been attributed to as saying "If sleep does not serve an absolutely vital function, then it is the biggest mistake the evolutionary process has ever made" (cited in MIGNOT 2008). The importance of sleep can be observed by the impact of chronic sleep restriction or total sleep deprivation in humans on a host of behavioral and physiological functions (e.g. BANKS and DINGES 2007). For example, one night of sleep deprivation results in a detrimental effect on cognitive function, particularly in tasks requiring executive function, emotion regulation, and decision-making (e.g. WALKER 2009). Furthermore, sleep deprivation not only impacts the brain, but also has consequences for the body – inadequate sleep has repercussions for weight gain and immune function (e.g. IMERI and OPP 2009, HANLON and VAN CAUTER 2011).

In-depth studies examining sleep regulation at cellular or neuronal levels have proven to be promising avenues for shedding light on the biological function of sleep. Such studies suggest that the functions of sleep include recovery at the cellular, endocrine system, and network levels, energy conservation and ecological adaptations, as well as a role in synaptic plasticity and learning to name a few (reviewed in MIGNOT 2008).

In the following section we focus on a few of the most prominent theories about the function of sleep, with the caveat that all theories are just that — theories. Although sound scientific evidence exists supporting each theory, these theories do not address all aspects of observed phenomena and are unable to reconcile some of the observed data.

The first hypothesis postulates that the slow components in the EEG underlie the restorative function of sleep. This hypothesis, called the synaptic homeostasis hypothesis, first articulated by Tononi and Cirelli proposes that slow oscillations present during non-REM sleep achieve synaptic homeostasis (TONONI and CIRELLI 2003; 2006). In their model, synaptic strength is high at the beginning of the night, due to plastic processes occurring during waking, and decreases by means of synaptic downscaling during sleep. This hypothesis is increasingly being supported by experimental evidence (e.g. HUBER *et al.* 2004, 2006; RIEDNER *et al.* 2007; VYAZOVSKIY *et al.* 2007, 2008), yet it is not without its critics (e.g. FRANK 2012).

Along the same lines as the synaptic homeostasis hypothesis, some have hypothesized that sleep is critical for learning and memory consolidation (RASCH and BORN 2013). This hypothesis is based on the observation from a large number of experimental studies showing that several memory tasks

show either an enhancement or lack of deterioration following a night of sleep as compared to a waking interval of the same duration. One limitation of this line of research is that the overnight gains in memory are small, typically on the order of a few words in a word-pair association task raising questions about whether the overnight learning/memory consolidation is perhaps only one of the many functions of sleep.

More recently VYAZOVSKIY and HARRIS (2013) proposed that sleep's primary function, in particular that of non-REM sleep, is to allow individual neurons to perform prophylactic cellular maintenance. They suggest that periods of reduced synaptic input ('off periods' or 'down states') are necessary for such maintenance. To allow this upkeep to occur would require a state of globally synchronized neuronal inactivity reflected in the occurrence of slow waves, reduced sensory input and behavioral immobility — the well-known manifestations of non-REM sleep.

Sleep may play a crucial role in organizing or reorganizing neuronal networks of the brain towards states with optimized information processing, i.e. critical dynamical states characterized by balanced activity patterns (MEISEL *et al.* 2013). MEISEL *et al.* (2013) demonstrated that signatures of criticality are progressively disturbed during wakefulness and restored by sleep. Thus, sleep may be important to reorganize cortical network dynamics to a critical state to ensure optimal computational functioning for the following time awake (MEISEL *et al.* 2013).

Though in recent years there has been much speculation about the function of non-REM sleep and particular oscillations during this sleep state (e.g., SWA), fewer hypotheses have addressed the role of REM sleep. A variety of functions have been proposed for REM sleep, including playing an active role in development (ROFFWARG *et al.* 1966), processing of emotional information (GUJAR *et al.* 2011, BARAN *et al.* 2012), and memory formation (e.g., SMITH 1985, KARNI *et al.* 1994, STICKGOLD 1998, WATTS *et al.* 2012, PEROGAMVROS *et al.* 2013, RASCH and BORN 2013). The latest hypothesis proposed by VYAZOVSKIY and DELOGU (2014) suggests that during REM sleep the degree to which homeostasis has been achieved during non-REM sleep is tested in different brain networks.

Humans' interest in sleep and its function has a long history and we have learned much since Aristotle first wrote his treatise "On Sleep and Sleeplessness" (written 350 B.C.E). We now know that sleep is a homeostatic process in all species studied. Sleep deprivation not only impacts the functioning of an organism across many domains, but also, leads to an increase in sleep duration and intensity. Furthermore, through slow wave activity, we have a measure, that increases with sleep loss and is an index of sleep depth. However, despite all our progress regarding the function of sleep and the mechanisms by which sleep washes away the waking day and restores equilibrium, the fundamental purpose of sleep remain elusive and mysterious.

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HUMAN SLEEP AND ITS REGULATION

Summary

Every night we give ourselves over to sleep. Observing a sleeping person one might mistakenly think that sleep is a time of inactivity for the body and brain. However, this is far from true. During sleep the brain is buzzing with activity and cortical oscillations emerge that can only be seen while asleep. In this article we discuss methods used to capture brain activity during sleep, and focus on a cortical oscillation called the slow wave. Slow waves are low frequency high amplitude waves that reflect the sleep homeostatic processes — they track the amount of prior sleep and wakefulness, increasing with time awake and decreasing during sleep. We discuss how these waves have been used to model the homeostatic sleep process. Finally, we conclude by giving an overview of a few of the most prominent theories about the functions of sleep.

LUDZKI SEN I JEGO REGULACJA

Streszczenie

Każdą noc poświęcamy na sen. Obserwując osobę śpiącą, można błędnie sądzić, że sen jest czasem bezczynności dla ciała i mózgu. Jednak przypuszczenie to jest dalekie od prawdy. Podczas snu mózg tętni aktywnością i co więcej pojawiają się wtedy charakterystyczne tylko dla snu korowe oscylacje jego czynności bioelektrycznej. W artykule tym omawiamy metody wykorzystane do poznania aktywności mózgowej podczas snu, koncentrując się na oscylacji korowej, którą nazywamy falą wolną. Fale wolne cechują się niską częstotliwością i wysoką amplitudą, która odzwierciedla procesy homeostazy snu. Innymi słowy, ich amplituda jest miarą ilości wcześniejszego snu i/lub czuwania, wzrastając z czasem czuwania, a zmniejszając się podczas snu. Wyjaśniamy w jaki sposób te fale zostały użyte w modelu homeostatycznej regulacji snu. W końcu, przedstawiamy kilka fundamentalnych teorii o funkcjach snu.

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